

Research Study Informed Consent Document for PBTC-055 Phase I Stratum 1

Study Title for Participants:

Testing the safety of adding hydroxychloroquine to dabrafenib and trametinib in children with either a low grade or high grade brain tumor with a specific (V600) genetic mutation previously treated with similar drugs who did not respond completely or their tumor came back while receiving a similar agent.

Official Study Title for Internet Search on <http://www.ClinicalTrials.gov>: PBTC-055: Phase I/II trial of Dabrafenib, Trametinib, and Hydroxychloroquine (HCQ) for BRAF V600E-mutant or Trametinib and HCQ for BRAF fusion/duplication positive or NF1-associated recurrent or refractory gliomas in children and young adults.

Overview and Key Information

You are being asked to take part in a research study of an experimental combination of drugs for brain tumors that have come back after other treatment. Research studies only include people who choose to take part. We are asking if you want to participate in this study because there is not a proven treatment for your brain tumor. This consent form gives you information about this study. Please read the consent form carefully and take time to make the decision about whether to participate. You may discuss this decision with your family and friends. If there are any questions, ask your study doctor *Physician's name* at *Physician's telephone number* or health care team for more explanation. No study procedure will be done until after you sign this form. You will be given a copy of it to keep if you decide to participate in this study.

This research is studying the combination of the drugs dabrafenib and trametinib plus hydroxychloroquine. The purpose of the research is to see if this combination is safe and tolerated without severe side effects in children.

The combination of dabrafenib and trametinib has been used in adults and some other childhood cancers. This combination plus hydroxychloroquine is considered research because it has not been proven to work in a brain tumor like yours. There is some evidence to believe it may work against brain tumors. However, we have not yet found the safe dose for children or proven that the combination works for brain tumors. This study may help the study doctors learn things that may help other people in the future

Patients in the Phase I portion of this study, will be divided into two groups based upon their type of brain tumor which will determine the combination of study drugs you take during this study. Patients in Group 1 (called Stratum 1) are patients with low grade or high grade brain tumor who have a specific genetic marker in their tumor tissue. These patients will receive Dabrafenib and Trametinib plus Hydroxychloroquine.

Patients in Group 2 (called Stratum 2) are patients with low grade brain tumor who have a genetic change in their tumor (a change in the BRAF gene) but do not have neurofibromatosis type 1 (NF-1) or have a low grade glioma and a diagnosis of NF-1. Neurofibromatosis is an inherited genetic

condition that causes tumors to grow on nerve tissue. These patients will receive Trametinib plus Hydroxychloroquine.

If you decide to participate in this study, you could continue for as long as 2 years. During that time, you would need to see your study doctor every week during the first course (28 days) and every 4 weeks for the rest of the study courses. During your study visits, you will have exams, tests and procedures to help your doctor closely monitor your safety and health. If you experience bad effects, you might have to return more frequently or even be in the hospital. The most common risks for this study are nausea, fatigue, diarrhea, rash and eye problems.

There will be no direct benefit to you from participating in the study. However, this study will help doctors learn more about brain tumors, and it is hoped that this information will help in the treatment of future patients with conditions like yours.

If you decide not to participate in this research, your other choices may include:

- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting no treatment

This research study is being done by the Pediatric Brain Tumor Consortium (PBTC) in collaboration with a pharmaceutical company who will provide two of the drugs. The PBTC is a group that is dedicated to improving treatment of childhood brain tumors. It is made up of eleven academic centers and children's hospitals in the United States.

What am I being asked to do?

We are asking you to take part in a research study. This study has public funding from the National Cancer Institute (NCI), part of the National Institutes of Health (NIH) in the United States Department of Health and Human Services. We do research studies to try to answer questions about how to prevent, diagnose, and treat diseases like cancer.

We are asking you to take part in this research study because you have a low-grade glioma or high-grade glioma with a certain tumor marker that has grown or has come back after receiving a similar drug.

Taking part in this study is your choice.

You can choose to take part, or you can choose not to take part in this study. You also can change your mind at any time. Whatever choice you make, you will not lose access to your medical care or give up any legal rights or benefits.

This document has important information to help you make your choice. Take time to read it. Talk to your doctor, family, or friends about the risks and benefits of taking part in the study. It's important that you have as much information as you need and that all your questions are answered. See the "Where can I get more information?" section for resources for more clinical trials and general cancer information.

Why is this study being done?

This study is being done to answer the following question:

Is the combination of dabrafenib and trametinib plus hydroxychloroquine safe and tolerated without severe side effects in children?

We are doing this study because we want to find out if this approach is better or worse than the usual approach for your recurrent or progressive brain tumor. The usual approach is defined as care people get for recurrent or progressive glioma..

What is the usual approach to my low-grade glioma or high-grade glioma?

The usual approach for patients who are not in a study is treatment with surgery, radiation, or drugs but there is not a Food and Drug Administration (FDA) approved treatment. Sometimes, combinations of these treatments are used. Your doctor can explain which treatment may be best for you. These treatments can reduce symptoms and may stop the tumor from growing for a few months or longer.

What are my choices if I decide not to take part in this study?

- You may choose to have the usual approach described above.
- You may choose to take part in a different research study, if one is available.
- You may choose not to be treated for cancer.
- You may choose to only get comfort care to help relieve your symptoms and not get treated for your cancer.

What will happen if I decide to take part in this study?

If you decide to take part in this study, you will take dabrafenib and plus hydroxychloroquine twice a day and trametinib once a day for a 28-day course. You will continue to repeat these 28-day courses for up to 2 years as long as your brain tumor doesn't grow.

After you finish taking dabrafenib and trametinib plus hydroxychloroquine, your doctor and study team will watch you for side effects up to 5 years from the start of treatment. They will check you every 3 months during the follow-up.

What are the risks and benefits of taking part in this study?

There are both risks and benefits to taking part in this study. It is important for you to think carefully about these as you make your decision.

Risks

We want to make sure you know about a few key risks right now. There is more information in the "What possible risks can I expect from taking part in this study?" section.

If you choose to take part in this study, there is a risk that the study drugs may not be as good as the usual approach for your cancer at shrinking or stabilizing your cancer.

There is also a risk that you could have side effects from the study drugs. These side effects may be worse and may be different than you would get with the usual approach for your cancer.

Some of the most common side effects that the study doctors know about are:

- Nausea
- Fatigue
- Diarrhea
- Rash
- Eye problems

There may be some risks that the study doctors do not yet know about.

Benefits

There is some evidence in people with another cancer that giving hydroxychloroquine with dabrafenib and trametinib can shrink or stabilize cancer. However, we do not know if this will happen in people with your type of cancer. It is unlikely that it will work in everyone with your cancer or help you live longer. This study may help the study doctors learn things that may help other people in the future.

If I decide to take part in this study, can I stop later?

Yes, you can decide to stop taking part in the study at any time.

If you decide to stop, let your study doctor know as soon as possible. It's important that you stop safely. If you stop, you can decide if you want to keep letting the study doctor know how you are doing.

Your study doctor will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

Are there other reasons why I might stop being in the study?

Yes. The study doctor may take you off the study if:

- Your health changes and the study is no longer in your best interest.
- New information becomes available and the study is no longer in your best interest.
- You do not follow the study rules.
- If you become pregnant while on the study.
- The study is stopped by the National Cancer Institute (NCI), Institutional Review Board (IRB), Food and Drug Administration (FDA) or the Pediatric Brain Tumor Consortium (PBTC). The study sponsor, (PBTC) is the organization who oversees the study.

It is important that you understand the information in the informed consent before making your decision. Please read, or have someone read to you, the rest of this document. If there is anything you don't understand, be sure to ask your study doctor or nurse.

What is the purpose of this study?

The purpose of this part of the study is to test the safety of adding hydroxychloroquine to dabrafenib and trametinib. This study tests different doses of the drug Hydroxychloroquine to see which dose is safer for children. The combination of dabrafenib and trametinib has been approved

by the FDA to treat other cancers in adults. Hydroxychloroquine has been approved by the FDA to treat malaria, a form of arthritis and a similar disease called Lupus.

There will be about 75 people total taking part in this study.

What are the study groups?

Patients in Stratum 1 will take dabrafenib and trametinib plus hydroxychloroquine. Approximately 12-20 patients will participate in this part of the study.

You will take dabrafenib and trametinib plus hydroxychloroquine by mouth every day for 28 days. A course is 28 days. This study has 26 courses. See the study calendar for more information.

The safe doses of dabrafenib and trametinib identified in an earlier study will be given to all patients. Different doses of hydroxychloroquine will be given to study participants. The first 2-6 people taking part in this part of the study will get the lowest dose. If the drugs do not cause serious side effects, the next group of people in the study will get a higher dose. The study doctor will watch each group carefully as they increase the dose. If the higher dose causes people to have serious side effects the dose will be lowered. Once the highest dose that does not have serious side effects is found, the dose escalation will be stopped.

Once the highest safe dose is found in the Phase I portion of the trial for the pediatric combination, patients who are still receiving treatment at a lower dose of hydroxychloroquine and whose brain tumors have not grown will have their dose increased. The dose of hydroxychloroquine will be increased to the highest safe dose identified for the remainder of the study for patients who have not had serious side effects at lower doses.

You will not be able to get additional doses of the drugs when the study ends. This drug combination is not approved by the FDA for treatment of your disease.

What exams, tests, and procedures are involved in this study?

Before you begin the study, your doctor will review the results of your exams, tests, and procedures. This helps your doctor decide if it is safe for you to take part in the study. If you join the study, you will have more exams, tests, and procedures to closely monitor your safety and health. Most of these are included in the usual care you would get even if you were not in a study.

Listed below are exams, tests, and procedures that need to be done as part of this study to monitor your safety and health but may not be included in the usual care. We will use them to carefully follow the effects of the study treatment, including preventing and managing side effects.

These exams, tests, and procedures to monitor your safety and health include:

- An Electrocardiogram (EKG) will be done prior to starting treatment, between 2-6 hours after the first dose and then every 3 months during treatment and at the end of treatment
- An Echocardiogram (ECHO) will be done prior to starting treatment, every 3 months during treatment and at the end of treatment

- Eye exams (assessing how well you see, looking at the back of your eye and measuring the thickness of the nerve that helps you see) will be done prior to starting treatment, every 3 months during treatment and at the end of treatment.

Your study doctor may recommend additional exams later during treatment if you have symptoms of heart or eye problems

Some exams, tests, and procedures are a necessary part of the research study but would not be included in usual care. Listed below are lab procedures that will be done for research purposes only.

- Autophagy Inhibition

You will need to have blood samples taken at specific time points for the study. These blood samples will be drawn from your arm or existing line before you start treatment, on Day 1 and Day 15 of Course 1, and at each time you have an MRI (if you have low-grade glioma, your MRIs will be at the end of courses 2,4,6, then every 3 months; if you have high-grade glioma, your MRIs will be every 2 months) and at the end of therapy. Autophagy inhibition looks at how your tumor cells are responding to the treatment. The study doctor will draw 12-15 ml or about 2 ½ to 3 teaspoons at each time point. You and your study doctor will not get the results of this testing.

- Circulating tumor DNA

You will need to have blood samples collected before you start treatment then on course 1 day 15 and with each scheduled MRI (if you have low-grade glioma your MRIs will be at the end of courses 2,4,6, then every 3 months; if you have high-grade glioma, your MRIs will be every 2 months) and at the end of therapy. The investigators would like to see if tumor markers can be seen in other sample types such as blood and if they can be used to tell how you are responding to treatment. The study doctor will collect about 10 ml (about 2 teaspoons) at each time point. You and your study doctor will not get the results of this testing.

- Pharmacokinetic (PK) and Pharmacogenetics blood specimen collection

You will need to have blood samples taken on Course 1 days 1, 2, 3, and 4, and on Course 2 day 1. Pharmacokinetics (PK) tests help the doctors understand how the body handles the study drugs. The researchers learn how much of these drugs stay in the blood by testing at specific different time points.

You can either choose to have multiple sticks, or have a temporary line placed in your arm to get these PK blood samples.

****It is important that you DO NOT TAKE your drugs on the days of PK draws listed below until after that day's PK blood draw. Your study doctor will tell you when to take the study drug(s) on these days. Please bring your medications with you.**

Beginning on Course 1 Day 1: For the dabrafenib PK sample, less than 1/4 teaspoon (about 1 ml) of blood will be collected each time before your first doses of dabrafenib. Then blood will be drawn 30 min 1hour, 2hours, 4hours, 8hours, and 24hours after the first dose administration.

Beginning on Course 1 Day 2: For the trametinib PK, sample, less than 1/4 teaspoon (about 1 ml) of blood will be collected each time before your first doses of trametinib. Then blood will be drawn 1 hour, 2hours, 4hours, 8hours, and 24hours after the first dose administration.

Beginning on Course 1 Day 2: For the hydroxychloroquine PK, sample, less than 1/4 teaspoon (about 1 ml) of blood will be collected each time before your first doses of hydroxychloroquine. Then blood will be drawn 1 hour, 2hours, 4hours, 8hours, and 24hours 32hours, and 48hours after the first dose administration.

Beginning on Course 2 Day 1: Blood samples for dabrafenib and trametinib pharmacokinetic studies will be collected at the following times: pre-dose, 1hour, 2hours , 4hours, 8hours, and 24hours after dose administration.

Beginning on Course 2 Day 1: Blood samples for hydroxychloroquine pharmacokinetic studies will be collected at the following times: pre-dose, 4hours, and 24hours after dose administration.

You will keep a drug diary for each medication you take. These diaries help you keep track of when you take your medication. The study doctor will show you how to use these diary. Each time you visit the clinic, you must bring the medication diaries, any remaining pills, and the medication bottles.

What possible risks can I expect from taking part in this study?

General Risks

If you choose to take part in this study, there is a risk that the study drugs may not be as good as the usual approach for shrinking or stabilizing your cancer.

You also may have the following discomforts:

- Spend more time in the hospital or doctor's office.
- Be asked sensitive or private questions about things you normally do not discuss.
- May not be able to take part in future studies.

The study drugs used in this study could be very harmful to an unborn or newborn baby. There may be some risks that doctors do not yet know about. It is very important that you check with your study doctor about what types of birth control or pregnancy prevention to use during the study and for 4 months after you have completed the study.

Side Effect Risks

The study drugs used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will test your blood and let you know if changes occur that may affect your health. There is also a risk that you could have other side effects from the study drugs.

Here are important things to know about side effects:

1. The study doctors do not know who will or will not have side effects.
2. Some side effects may go away quickly, some may last a long time, and some may never go away.

3. Some side effects may make it hard for you to have children.
4. Some side effects may be mild. Other side effects may be very serious and even result in death.

You can ask your study doctor questions about side effects at any time. Here are important ways to make side effects less of a problem:

- If you notice or feel anything different, tell your study doctor. He or she can check to see if it is a side effect.
- Your study doctor will work with you to treat your side effects.
- Your study doctor may adjust the study drugs to try to reduce side effects.

Drug Risks

The tables below show the most common and most serious side effects doctors know about. Keep in mind that there might be other side effects doctors do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

The different combination of these study drugs may increase your side effects or may cause new side effects.

Possible Side Effects of Dabrafenib

COMMON, SOME MAY BE SERIOUS
In 100 people receiving dabrafenib (GSK2118436B), more than 20 and up to 100 may have:
<ul style="list-style-type: none"> • Nausea • Tiredness • Fever (<i>Fever and complications of fever are more frequent and severe when dabrafenib mesylate is used together with trametinib dimethyl sulfoxide.</i>) • Pain • Headache • Hair loss • Skin changes including rash

OCCASIONAL, SOME MAY BE SERIOUS
In 100 people receiving dabrafenib (GSK2118436B), from 4 to 20 may have:
<ul style="list-style-type: none"> • Anemia which may require blood transfusion • Constipation, diarrhea, vomiting • Chills • Swelling of arms, legs • Flu-like symptoms including body aches • Cold symptoms such as stuffy nose, sneezing, sore throat • Bleeding (<i>The risk of bleeding is increased when dabrafenib mesylate is used together with trametinib dimethyl sulfoxide.</i>) • Infection, especially when white blood cell count is low • Loss of appetite

- A new skin cancer resulting from treatment of earlier cancer
- Wart
- Dizziness
- Cough
- Dry skin
- Change in hair
- Increased sweating
- Redness, pain or peeling of palms and soles
- Itching
- High blood pressure which may cause headaches, dizziness, blurred vision
- Blood clot which may cause swelling, pain, shortness of breath *(The risk is increased when dabrafenib mesylate is used together with trametinib dimethyl sulfoxide.)*

RARE, AND SERIOUS

In 100 people receiving dabrafenib (GSK2118436B), 3 or fewer may have:

- Swelling and redness of the eye
- Changes in the eyes that may cause blurred vision or blindness
- A tear or hole in the bowels that may require surgery
- Pain in belly (pancreas) that may require hospitalization
- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Fainting
- Kidney damage which may require dialysis *(The risk is increased when dabrafenib mesylate is used together with trametinib dimethyl sulfoxide.)*
- Skin rash developing 1-8 weeks after a drug is given which may be accompanied by fever, lymph node swelling and organ failure
- Swelling and redness of the skin
- Severe skin rash with blisters and peeling which can involve mouth and other parts of the body

Possible Side Effects of Trametinib

COMMON, SOME MAY BE SERIOUS

In 100 people receiving trametinib (GSK1120212B), more than 20 and up to 100 may have:

- Diarrhea, nausea
- Tiredness
- Swelling of the body
- Skin changes including rash, acne

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving trametinib (GSK1120212B), from 4 to 20 may have:

- Anemia which may require blood transfusion
- Abnormal heartbeat
- Blurred vision or other visual disturbances
- Dry eye, mouth, skin
- Swelling of the eye
- Pain
- Constipation, heartburn, vomiting
- Sores in the mouth which may cause difficulty swallowing
- Chills, fever
- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Infection
- Change in heart function
- Loss of appetite, dehydration
- Dizziness, headache
- Cough, shortness of breath
- Hair loss, itching
- Change in or loss of some or all of the finger or toenails
- High blood pressure which may cause headaches, dizziness, blurred vision
- Bleeding

RARE, AND SERIOUS

In 100 people receiving trametinib (GSK1120212B), 3 or fewer may have:

- Heart failure which may cause shortness of breath, swelling of ankles, and tiredness
- Changes in the eyes (blood clot or retinal detachment) which may cause blindness
- Blood clot which may cause swelling, pain, shortness of breath
- A tear or hole in the bowels that may require surgery
- Damage to muscle which may cause muscle pain, dark red urine
- Damage to the lungs which may cause shortness of breath
- Redness, pain or peeling of palms and soles
- Skin rash developing 1-8 weeks after a drug is given which may be accompanied by fever, lymph node swelling and organ failure
- Severe skin rash with blisters and peeling which can involve mouth and other parts of the body

Possible Side Effects of Hydroxychloroquine Sulfate

Very Common

Out of 100 people receiving hydroxychloroquine, more than 10 people may have:

- Abdominal Pain
- Nausea

Common

Out of 100 people receiving hydroxychloroquine, between 1 and 10 people may have:

- Headache
- Dizziness
- Blurry vision
- Changes in mood
- Diarrhea
- Vomiting
- Loss of appetite
- Skin rash
- Itching

Rare and Serious

Out of 100 people receiving hydroxychloroquine, less than 1 person may have:

- Dizziness
- Nervousness
- Ringing of the ears
- Liver damage
- Damage to the retinas of the eyes, which may cause a loss or change in vision, such as seeing spots or halos, abnormal colors, sensitivity to light, night blindness
- Sensory motor disorders, such as decreased coordination and balance, difficulties with taste, speech, touch, repetitive movements
- Pigmentary changes in skin and mucous membranes
- Bleaching of hair
- Alopecia

Additional Drug Risks

The study drug could interact with other drugs. Certain types of anti-seizure medications are not allowed while taking the study drugs. Your study doctor will review your current anti-seizure medication and if you are taking a medication that is not allowed, they can change your anti-seizure medication to another type that is allowed. Your study doctor will give you a drug information handout and wallet card that lists these possible interactions. Share this information with your family members, caregivers, other health care providers, and pharmacists.

What are my responsibilities in this study?

If you choose to take part in this study, you will need to:

- Keep your study appointments.
- Tell your doctor about:
 - all medications and supplements you are taking
 - any side effects
 - any doctors' visits or hospital stays outside of this study
 - if you have been or are currently in another research study
- Write down in your medication diary when you take the study drugs at home

For women: Do not get pregnant or breastfeed while taking part in this study. **For men:** Do not father a baby while taking part in this study. **For all:** Tell your study doctor right away if you

think that you or your partner have become pregnant during the study or within 4 months after your last dose of study drug.

What are the costs of taking part in this study?

You and/or your insurance plan will need to pay for other costs of medical care you get as part of the study, just as you would if you were getting the usual care for your cancer. This includes:

- the costs of tests, exams, procedures, and drugs that you get during the study to monitor your safety and prevent and treat side effects.
- the costs of getting the dabrafenib, trametinib and hydroxychloroquine ready and giving it to you.
- your insurance co-pays and deductibles.

Talk to your insurance provider and make sure that you understand what your insurance pays for and what it doesn't pay for if you take part in this clinical trial. Also, find out if you need approval from your plan before you can take part in the study.

Ask your doctor or nurse for help finding the right person to talk to if you are unsure which costs will be billed to you or your insurance provider.

You or your insurance provider will not have to pay for the dabrafenib, trametinib or hydroxychloroquine while you take part in this study.

Taking part in this study may mean that you need to make more visits to the clinic or hospital than if you were getting the usual approach to treat your cancer. You may:

- Have more travel costs.
- Need to take more time off work.
- Have other additional personal costs.

You will not be paid for taking part in this study. The research may lead to new tests, drugs, or other products for sale. If it does, you will not get any payment.

What happens if I am injured because I took part in this study?

If you are injured as a result of taking part in this study and need medical treatment, please talk with your study doctor about treatment options. The study sponsor will not pay for medical treatment for injury. Your insurance company may not be willing to pay for study-related injury. If you have no insurance, you would be responsible for any costs.

Novartis, the pharmaceutical company providing the study drugs, will not provide payment for any medical expenses which you may incur because of your participation in this study. No other type of compensation will be provided by Novartis.

If you feel this injury was a result of medical error on the part of the study doctors or others involved in the study, you have the legal right to seek payment even though you are in a study. Agreeing to take part in this study does not mean you give up these rights

Who will see my medical information?

Your privacy is very important to us. The study doctors will make every effort to protect it. The study doctors have a privacy permit to help protect your records if there is a court case. However, some of your medical information may be given out if required by law. If this should happen, the study doctors will do their best to make sure that any information that goes out to others will not identify who you are.

Some of your health information, such as your response to cancer treatment, results of study tests, and medicines you took, will be kept by the study sponsor in a central research database. However, your name and contact information will not be put in the database. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

There are organizations that may look at or receive copies of some of the information in your study records. Your health information in the research database also may be shared with these organizations. They must keep your information private, unless required by law to give it to another group.

Some of these organizations are:

- The study sponsor and any company supporting the study agents now or in the future. This would include any organization helping the sponsor with the study
- The NCI Central IRB, which is a group of people who review the research with the goal of protecting the people who take part in the study.
- Federal agencies such as the Food and Drug Administration, the Office of Human Research Protections (OHRP) and the National Cancer Institute in the U.S.
- Governmental agencies in other countries where the study drug may be considered for approval.
- Laboratories performing the required and optional research studies of blood and tumor samples.
- The pharmaceutical company that supplies dabrafenib and trametinib and any company supporting the study or the study agent now or in the future.
- Your insurance company or other health benefits plan (if charges are billed to these plans).

Coded patient data and images from brain scans will be transmitted over the internet to be analyzed by other PBTC researchers. The PBTC has procedures (data encryption) in place to make electronic transmission of research information as secure as possible. The data security involves coding the data in a way that only the authorized receiver can decode the data. The method used to transfer information is more secure than many methods used by financial institutions when conducting business over the internet.

In addition to storing data in the study database, data from studies that are publicly funded may also be shared broadly for future research with protections for your privacy. The goal of this data sharing is to make more research possible that may improve people's health. Your study records may be stored and shared for future use in public databases. However, your name and other personal information will not be used.

Some types of future research may include looking at your information and information from other patients to see who had side effects across many studies or comparing new study data with older study data. However, right now we don't know what research may be done in the future using your information. This means that:

- You will not be asked if you agree to take part in the specific future research studies using your health information.
- You and your study doctor will not be told when or what type of research will be done.
- You will not get reports or other information about any research that is done using your information.

There are laws that protect your genetic information. However, there is a risk that someone could get access to your genetic information and identify you by name. In some cases, employers could use your genetic information to decide whether to hire or fire you. The study doctors believe the risk of this happening is very small. However, the risk may increase in the future as people find new ways of tracing information. For more information about the laws that protect you, ask your study doctor.

Where can I get more information?

You may visit the NCI web site at <http://cancer.gov/> for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor *insert name of study doctor* at *insert telephone number, and email address if appropriate*.

For questions about your rights while in this study, call the *insert name of organization or center* Institutional Review Board at *insert telephone number*.

Optional studies that you can choose to take part in

This part of the consent form is about optional studies that you can choose to take part in. They are separate from the main study described above. These optional studies will not benefit your health. The researchers leading these optional studies hope the results will help other people with cancer in the future. The results will not be added to your medical records and you or your study doctor will not know the results.

Taking part in these optional studies is your choice. You can still take part in the main study even if you say "no" to any or all of these studies. There is no penalty for saying "no." You and your insurance company will not be billed for these optional studies. If you sign up for but cannot complete any of these studies for any reason, you can still take part in the main study.

Circle your choice of “yes” or “no” for each of the following studies.

Optional sample collections for known laboratory studies and/or storage for possible future studies

Researchers are trying to learn more about cancer and other health problems using blood and tissue samples from people who take part in clinical trials. By studying these samples, researchers hope to find new ways to prevent, detect, treat, or cure diseases.

Some of these studies may be about how genes affect health and disease. Other studies may look at how genes affect a person’s response to treatment. Genes carry information about traits that are found in you and your family. Examples of traits are the color of your eyes, having curly or straight hair, and certain health conditions that are passed down in families. Some of the studies may lead to new products, such as drugs or tests for diseases.

Known future studies

a. Genomics

If you choose to take part in this optional study, researchers will collect 5ml of blood (approximately 1 teaspoon) and a small piece of tumor tissue stored from a previous surgery for research on the chemical pathways associated with your type of tumor as well as looking for other genetic changes related to different cancer pathways. This study will require you to provide both the blood and tissue sample to increase the information learned from these tests.

Unknown future studies

If you choose to take part in this optional study a blood sample (approximately 1 teaspoon) and some of your stored tumor tissue which was removed during a previous study will be collected and stored. Storing samples for future studies is called “biobanking.” The biobank is being run by the Pediatric Brain Tumor Consortium and is supported by the NCI. This is a publicly funded study. Samples from publicly funded studies are required to be shared as broadly as possible. However, we will protect your privacy. The goal of this is to make more research possible that may improve people’s health.

Tissue, blood or CSF samples collected as a part of this study but not completely used for the analysis will be stored in the repository for future unspecified research. The researchers ask your permission to store and use your samples and related health information (for example, your response to cancer treatment, results of study tests and medicines you are given) for medical research. The research that may be done is unknown at this time.

The biobank is a public research resource. It has controlled access. This means that researchers who want to get samples and data from it must submit a specific research request. The request identifies who the researchers are and what their planned research project is. Before getting the samples and data, the researchers must agree to keep the data private, only use it for their planned research project, and never use it to try to identify you.

Right now, we don’t know what research may be done in the future using your samples. This means that:

- You will not be asked if you agree to take part in the future research studies.

- You and your study doctor will not be told when or what type of research will be done.
- You will not get reports or other information about any research that is done using your samples.

Unknown future research studies may include sequencing of all or part of your DNA. This is called genomic sequencing. Sequencing allows researchers to identify your genetic code. Changes in your genetic code may just be in your tumor tissue. These are called somatic changes. Changes may also be in your normal tissue and passed down through your family. For example, these genetic changes may be passed down to your children in the same way that eye and hair color are passed down. These are called germline changes. If only tumor tissue is sequenced, we will not know if a genetic change in your tumor is also in your normal tissue. This is why sometimes both normal tissue and tumor tissue are sequenced. This helps researchers understand if a genetic change happened only in your cancer tissue, or in your normal tissue as well.

What is involved in this optional sample collection?

If you agree to take part, here is what will happen next:

1. About 2 teaspoons of blood will be collected from a vein in your arm. A sample from the tissue that was collected at the time of your previous surgery will be sent to the biobank.
2. There is no limit on the length of time we will keep your samples and research information. The samples will be kept until they are used for research or destroyed.
3. Researchers can only get samples from the biobank after their research has been approved by experts. Researchers will not be given your name or contact information.
4. Some of your genetic and health information may be placed in central databases for researchers to use. The databases will not include your name or contact information.

What are the risks in this optional sample collection?

- The most common risks related to drawing blood from your arm are brief pain and maybe a bruise.
- Generally, hospitals will keep some of your tissue. This tissue may be used to help treat your cancer in the future. There is a small risk that when this tissue sample is submitted to the biobank for this optional sample collection, your tissue could be used up.
- Your medical and genetic information is unique to you. There is a risk that someone outside of the research study could get access to your study records or trace information in a database back to you. They could use that information in a way that could harm you. Researchers believe the chance that someone could access and misuse your information is very small. However, the risk may increase in the future as people find new ways of tracing information.
- In some cases, this information could be used to make it harder for you to get or keep a job and get or keep health insurance. There are laws against the misuse of genetic information, but they may not give full protection. For more information about the laws that protect you, ask your study doctor or visit: <https://www.genome.gov/10002328/>

How will information about me be kept private?

Your privacy is very important to the study researchers and biobank. They will make every effort to protect it. Here are just a few of the steps they will take:

1. They will remove identifiers, such as your initials, from your sample and information. They will replace them with a code number. There will be a master list linking the code numbers to names, but they will keep it separate from the samples and information.
2. Researchers who study your sample and information will not know who you are. They also must agree that they will not try to find out who you are.
3. Your personal information will not be given to anyone unless it is required by law.
4. If research results are published, your name and other personal information will not be used.

What are the benefits to taking part in this optional sample collection?

You will not benefit from taking part. The researchers, using the samples from you and others, might make discoveries that could help people in the future.

Are there any costs or payments to this optional sample collection?

There are no costs to you or your insurance. You will not be paid for taking part in this study. The research may lead to new tests, drugs, or other products for sale. If it does, you will not get any payment.

What if I change my mind about this optional sample collection?

If you decide you no longer want your samples to be used, you can call the study doctor, *insert name of study doctor for main trial*, at *insert telephone number of study doctor for main trial*, who will let the biobank know. Then, any sample that remains in the biobank will be destroyed or returned to your study doctor. This will not apply to any samples or related health information that have already been given to or used by researchers.

What if I have questions about this optional sample collection?

If you have questions about the use of your samples for research, contact the study doctor, *insert name of study doctor for main trial*, at *insert telephone number of study doctor for main trial*.

Please circle your answer below to show if you would or would not like to take part in each optional study:

Samples for known future studies

I agree that my samples and related information may be used for the laboratory study (ies) described above.

YES _____ NO _____

Samples for unknown future studies

I agree that my samples and related information may be kept in a biobank for use in future health research..

YES _____ NO _____

This is the end of the section about optional studies.

My signature agreeing to take part in the study

I have read this consent form, or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed and dated copy of this form. I agree to take part in the main study. I also agree to take part in any additional studies where I circled and initialed “yes”.

Participant’s signature

Date of signature

Parent or Legal Guardian Signature

Date of Signature

2nd Parent or Legal Guardian

If permission by both parents is required, both signatures should be completed unless one parent is deceased, unknown, incompetent, not reasonably available, or only one parent has legal responsibility for the care and custody of the child.

Date of Signature

Signature of person(s) conducting the informed consent discussion

Date of signature

Appendix A: Study Calendar for Phase I

	Pre-treatment	Course 1	Course 1 Day 15	Courses 2- Course 13 (+/- 7 days)	Courses 14-26 (+/- 7 days)	Completion/ Discontinuation Of Treatment (within 30 days of the last dose)
Physical Assessments						
Medical history	X	Weekly		X	X	X
Physical exam/height/weight/skin exam	X	Weekly		X	X	X
Vital signs	X	Weekly		X	X	X
Performance status	X			X	X	X
Neurologic exam	X	Weekly		X	X	X
Laboratory Evaluations						
Blood Counts	X	Weekly		X ^A	Every 8 weeks	X
Blood Chemistries including liver enzymes	X	X		X ^A	Every 8 weeks	X
Serum or Urine pregnancy test (for females of childbearing potential)	X	X		X	X	
CSF cytology (if clinically indicated)	X					
Evaluations						
Echocardiogram (ECHO)	X			X	X	X
Electrocardiogram (ECG)	X	X		X	X	
Eye Exam	X			X	X	X
Imaging Assessments						
Brain MRI low-grade glioma	X			Every 8 weeks (end of courses 2,4,6) and then every 12 weeks.		X
Brain MRI high-grade glioma	X			Every 8 weeks		
Spinal MRI (only if clinically indicated)	X			X	X	X
Research Samples						
Biomarkers	X		X	With each MRI	With each MRI	
Pharmacogenetics and Pharmacokinetics	X	X				